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09/423,351	05/10/2000	KEITH WILLISON	MEWBURN	6633

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,351	WILLISON ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *20-37 and 40-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-19 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Acknowledgment is made of applicants election with traverse of Group I, drawn to a method of identifying a binding member capable of occupying a substrate binding site on the CCT complex or part thereof and a method of screening fro mimetics to the aforesaid binding members. the traversal is on the grounds that the restriction is improper because it relies on lack of unity over WO 93/25681 and WO 98/24909. The examiner concurs with applicant, that WO 93/25681 and WO 98/24909 do not anticipate the claims of the instant invention. However lack of unity is maintained in light of the art rejections below, and further in light of Kim et al (Trends in Biomedical Sciences, 1994, Vol. 19, pp. 543-548) wherein it is disclosed that actin binds to CCT complex (page 547, second column, lines 42-47, thus fulfilling the specific embodiments of claims 20-24. It is noted that applicants arguments regarding the requirement that inventions be both independent and distinct in the case of a filing under 35 USC 121 is irrelevant to the instant application which was filed under 35 USC 371, and further is also incorrect. Section 806 of the MPEP teaches

> The general principles relating to distinctness or independence may be summarized as follows:
> (A) Where inventions are independent (i.e., no disclosed relation there between), restriction to one thereof is ordinarily proper, MPEP § 806.04 - § 806.04(i), though a reasonable number of species may be claimed when there is an allowed (novel and unobvious) claim generic thereto. 37 CFR 1.141, MPEP § 809.02 - § 809.02(e).
> (B) Where inventions are related as disclosed but are distinct as claimed, restriction may be proper.

It is clear from the MPEP that the inventions need only be independent **or** distinct, and that there is not requirement for the showing of independence **and** distinctness.

Claims 1-43 are pending. claims 20-37 and 40-43, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-19 and 31-37 are examined on the merits.

Claims 31 and 35, and dependent claims 31-34 and 36-39 are objected to for being dependent upon non-elected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 31-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "a binding member capable of occupying a substrate binding site on the CCT complex...wherein the binding member inhibits the binding of the CCT substrate and the CCT complex". It is unclear if the "binding member capable of occupying a binding site on the CCT complex or part thereof is inhibiting the binding of the CCT substrate to the CCT complex because the claim states that the binding of the CCT substrate and the CCT complex is inhibited, but does not state that the binding of the CCT substrate to the CCT complex is inhibited and thus reads on the inhibition of the binding of the CCT complex to another molecule which is not the CCT substrate.

The recitation of "substrate" in claims 7 and 8 renders the claims vague and indefinite because it is not clear if "the substrate" is that from which the binding member is derived, (claim 6), or if "the substrate" refers to "the CCT substrate" of claim 1.

Claim 11 is vague and indefinite in the recitation of "determining binding between said candidate binding member and the CCT apical domain". It is unclear if "determining" is directed to a quantitative or qualitative measurement.

It is unclear how claim 13 further limits claim 12 and how claims 14 and 15 further limits claim 13 claim 11 is drawn to a method for identifying a binding member comprising contacting a candidate binding member with a CCT apical domain and determining the binding of said member and the CCT apical domain. Claim 12 embody the method of claim 11 wherein the binding member is selected from the group consisting of a peptide or a peptide fragment. Claim 13 embodies the method of claim 12 wherein the candidate binding member is a peptide or peptide fragment having an amino acid sequence corresponding to the apical domain. However, the requirement inherent in claim 12 is that the peptide or peptide fragment must bind to the apical domain. Having the specific limitation of the peptide or peptide fragment having an amino acid sequence corresponding to the apical domain would preclude the peptide from

binding to the apical domain. Claims 14 embodies the method of claim 13 wherein the CCT substrate is actin. This would appear to be inherent in claim 13 because it is taught in the art that the CCT substrate is indeed actin. Claim 14 embodies the method of claim 14 wherein the CCT substrate is tubulin. This contradicts the limitation of claim 13 wherein the CCT substrate is actin. Further, it is known in the art that actin is also a substrate o the CCT complex, and it is unclear how recitation of the known substrates of the CCT complex further limits the scope of claim 13.

Claim 31 fails to relate the extent of binding of the candidate mimetic to the CCT substrate biding site with the method of objective of screening for mimetics.

Claims 3, 12, 13, recite peptide or peptide fragment. The metes and bound of what constitutes a peptide fragment is unclear. A peptide is defined in the art as two or more amino acids joined by a peptide bond. Thus, a peptide fragment could be a single amino acid or part of an amino acid.

Claims 9, 16 are vague and indefinite in their dependence upon Figure 9. The MPEP 2173.05(s) Reference to Figures or Tables

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference
>
> is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Claim 31 is unclear as to what constitutes the "active portion thereof" as the activity is not defined in terms of a function.

Claim 32 is vague and indefinite in the recitation of "screening...for biological activity" without a definition of biological activity which would define the metes and bounds of "biological activity"

Claim 36. It is unclear what constitutes the "CCT substrate binding site complex or active portion thereof". It is unclear if this aforesaid complex includes a substrate molecule as the complex is referred to as a CCT substrate binding site, which refers to CCT, not the substrate. Further. it is also unclear what constitutes the "active portion thereof" as the activity is not defined in terms of a function. Further the metes and bounds of claim 36 with regard to the dependence upon the product of claim 27 is unclear.

Claims 1-3, 6, 7, 8, 11, 19 and 31-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a method for identifying a binding member capable of occupying a substrate binding site on the CCT complex or part thereof wherein he binding member inhibits the binding of the CCT substrate and the CCT complex. Claim 2 embodies the method of claim 1 wherein the binding member is an antibody. claims 3-5 specify that the binding member is a peptide or a peptide fragment. claim 7 is included with this group because it is unclear if the limitation of actin, tubulin or cyclin further limits the CCT substrate of the binding member according to the rejection set forth under 112, second paragraph above. Claim 11 is drawn to a method of identifying a binding member capable of occupying a substrate binding site on a CCT apical domain comprising the steps of contacting a candidate binding member with said CCT apical domain. Claim 19 embodies the method of claim 11 wherein the binding is determined by a competitive assay. Claims 31 is drawn to a method for screening for mimetics of binding members comprising exposing claimed binding members and a candidate mimetic to a CCT substrate binding site or active portion thereof so that the candidate mimetic and the binding member compete to bind to the CCT substrate binding site. Claim 32 embodies the method of claim 31 wherein the candidate mimetic is further screened for biological activity. claim 33 specifies that the biological activity is cytoskeletal activity. claim 34 specifies that the biological activity is CCT complex dis-assembly. Claims objected to for being dependent on anon-elected

claims are included with this rejection because it is unclear what the claims are actually encompassing.

The specification teaches various peptides derived from actin as inhibitors of the folding to actin in vivo (page 47, line 6 to page 52, line 27). the specification has identified actin, tubulin and the cyclins as substrates for the CCT complex (page 55, lines 14-15, 21-25). The above claims are dependent upon a genus of binding members which are capable of occupying a substrate binding site on the CCT complex, and methods of screening for mimetics of said binding members. When given the broadest reasonable interpretation, the binding members read on proteins, peptides, antibodies and any other non-peptide based molecule which can bind to CCT and inhibit the binding of a CCT substrate. The genus is highly variant because it encompasses molecules which are not structurally related to the peptide fragments of actin, tubulin and cyclins, or the antibodies which bind to the substrate binding sites of actin, tubulin and cyclins. It is noted that the specification defines a "functional mimetic" as encompassing molecules which are not peptides. The art teaches that actin and tubulin bind at the apical domain of the CCT complex, and thus the requirement for written description of an antibody which binds to the apical domain is not high in view of what is known in the art. However, the specification teaches that biding of CCT to cyclins differs from the binding of CCT to tubulin or actin (page 55, lines 21-25) , thus it would not be expected that an antibody which inhibited the binding of tubulin of actin to CCT would inhibit the binding of any cyclin to CCT. The disclosed genus of peptide fragments of actin which are binding members for the CCT complex, does not adequately describe this genus, because the genus includes molecules which are not peptide based. Further, antibodies which bind to the apical domain do not adequately describe the genus of antibodies which bind to the binding site for cyclins because the antibodies which were inhibitors of actin or tubulin binding to CCT would not be expected to bind to the epitopes on CCT where antibodies which wherein inhibitors of cyclin would bind. Because the binding members on which the instant method claims depend are not adequate described it follows that methods depending on said binding members are also not adequately described. .

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substrate binding site on the apical domain of the CCT complex, does not reasonably provide enablement for a substrate binding site on the CCT complex or part

thereof which is not the apical domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification and the art teach that the binding site for actin and tubulin is on the apical domain of the CCT complex. The specification teaches on page 55, lines 21-25 that cyclins E, D1 and D2 are specific binding partners for CCT but that the binding kinetics are different from the kinetics for the folding of actin and tubulin, thus it would be reasonable to conclude that cyclins E, D1 and D2 bind to a different part of the CCT complex than actin or tubulin. The specification fails to teach a binding site on the CCT complex which is not the apical domain as taught in the art. Therefore, one of skill in the art would be subject to undue experimentation in order to practice the invention to the full scope of the claims to "part thereof" in reference of the "binding site".

Claims 31-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mimetics to the binding members disclosed as the BEP peptides, does not reasonably provide enablement for binding members which have not been disclosed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The instant claims are drawn to methods for identifying mimetic of the binding members which inhibit the binding of the CCT complex and the CCT substrate. In order to carry out the claimed methods it would be necessary to be able to make the binding members to be able to identify compounds which are mimetics of said binding members. However, the instant specification does not teach how to make said binding members other than the BEP epitopes (page 47, line 6 to page 52, line 27). The examiner notes that teaching how to identify binding members by means of the disclosed assay on CCT, is not equivalent to teaching how to make the binding members. thus, one of skill in the art would be subject to undue experimentation in order to carry out the broadly claimed methods because one of skill in the art would first be required to identify the binding members and them further identify the mimetics.

Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the apical domain as identified as the tertiary structure which

corresponds to the tertiary structure of the GroELcomples, formed from residues 190-377 in the primary structure of GroEL (Kim et al, Trends in Biochemical Sciences, 1994, Vol. 19, pp. 543-548, on page Figure 2b and Figure 3 (b and d) does not reasonably provide enablement for any other undisclosed apical domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 13 embodies the limitation of "a CCT apical domain" which implies that there is more than one apical domain on CCT. In light of the prior art which identifies only one apical domain as corresponding to the tertiary structure of the apical domain of the GroEL complex (Kim et al, 1994, ibid, Figure 3), the specification provides no teachings to address the presence of more than one apical domain. One of skill in the art would be subject to undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al (Trends in Biochemical Sciences, 1994, Vol. 19, pp. 543-548). Claim 11 is drawn to a method of identifying a binding member capable of occupying a substrate binding site on a CCT apical domain comprising the steps of contacting a candidate binding member with said CCT apical domain and determining the binding between said candidate binding member and the CCT apical domain. Claim 12 is drawn in part to the method of claim 11 wherein the binding member is a peptide.

Kim et al disclose a method for determining the binding member to the CCT apical domain comprising contacting the CCT complex comprising the apical domain with actin, and determining that actin binds to said CCT apical domain (page 547, second column, lines 42-47)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 6 and 7, are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (Abstract from the 9th International Congress on Immunology, 1995, page 671, abstract # 3982) as evidenced by Kubota et al (Gene, 1995, Vol. 154, pp. 231-236)in view of Hynes et al (Electrophoresis, 1996, Vol. 17, pp. 1720-1727).

Claim 1 is drawn to a method for identifying a binding member capable of occupying a substrate binding site on the CCT complex or part thereof wherein the binding member inhibits the binding of the CCT substrate and the CCT complex. Claim 3 embodies the method of claim 1 wherein the binding member is a peptide. Claim 4 embodies the method of claim 3 wherein the binding member is greater than 5 amino acids. Claim 6 embodies the method of claim 3 wherein the binding member is derived from a CCT substrate. claim 7 embodies the method of claim 6 wherein the substrate is actin, tubule or cyclin. Claim 8 embodies the method of claim 7 wherein the substrate is actin.

Smith et al teach that Inflame and TGF induced melanoma cells to synthesize two proteins characterized by Molecular Weight /pin ratios of 20/5.6 and 32/54. Smith et al teach that the sequence analysis of these two proteins indicated homology to the N-terminal of alpha

tubulin. Smith et al teach a correlation between the appearance of the aforesaid proteins and the decrease in alpha tubulin. Smith et al teach that levels of TCP-1 were also suppressed upon appearance of the two new proteins Smith et al conclude that folding and assembly of tubulin is altered in melanoma cells treated with TNF or TNF in combination with INFgamma. Smith et al further conclude that an antiproliferative response will result from the administration of TNF or TNF and INFgamma because it is recognized that tubulin has an important role in cell growth and replication.

Kubota et al teach that TCP-1 is synonymous with the theta subunit of CCT (abstract).

Hynes et al teach that transformed cells exhibit an increased rate of actin and tubulin synthesis , and because tubulin and actin are substrates of CCT, the upregulation of CCT would be required to mediate the elevated amounts of actin and tubulin synthesis necessitated by the transformed state (page 1723, column 2, lines 12-17 under the heading of "Differential expression in normal, transformed and psoriatic keratinocytes").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to determine if the proteins produced by the melanoma cells in response to TNF or TNF and INFgamma inhibited the binding of the tubulin to the CCT complex by contacting the CCT complex with either melanoma protein in combination with tubulin. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Smith et al suggesting the appearance of the melanoma proteins of 20/5.6 and 32/5.4 in response to TNF or TNF and INFgamma occurred with the concomitant decrease in TCP-1 and alpha tubulin. It is suggestive of the teachings of Smith et al that the aforesaid proteins induced upon exposure to cytokines were in competition with TCP-1 for the unfolded tubulin substrate and that upon decreased folding of tubulin TCP-1 itself was downregulated. Thus it appears that the synthesis of the new melanoma proteins in response to TNF and INFgamma causes a negative feedback loop[resulting in the downregulation of alpha tubulin synthesis resulting in a decreased proliferation. One of skill in the art would be motivated to find binding members which competed with tubulin to cause decreased tubulin and actin synthesis to negatively control the increased demands for actin and protein synthesis imposed by the transformed state as taught by Hynes et al. Claim 8 is included with this rejection because it is not clear if the recitation of "the substrate is actin" refers to the substrate

from which the binding member is derived (claim 6) or if it refers to the "CCT substrate" in claim 1". Because Hynes et al teach that actin is a substrate of CCT, it fulfills the specific embodiments of claim 8.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
11/17/03